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A study of the neuropsychological correlates in adults with high functioning autism spectrum disorders

Fried R, Joshi G, Bhide P, Pope A, Galdo M, Koster, A, Chan J, Faraone S, Biederman J. A study of the neuropsychological correlates in adults with high functioning autism spectrum disorders.

Objective: To examine the unique neuropsychological presentation in adults with high functioning autism spectrum disorders (HF-ASD) by comparison with adults with attention deficit hyperactivity disorder (ADHD).
Methods: Adults with ASD referred to a specialty clinic ($n = 26$) were compared to two non-ASD groups with ($n = 52$) and without ($n = 52$) ADHD of similar age and sex.
Results: No differences in IQ were found. Subjects with HF-ASD were significantly more impaired than both comparison groups in processing speed, cognitive flexibility and sight words. Subjects with HF-ASD were more impaired than controls in working memory, but not the ADHD group.
Conclusion: These findings suggest that there may be specific neuropsychological correlates of HF-ASD differing from ADHD that could have significant implications for identifying individuals at risk for ASD.

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Keywords: ADHD; autism spectrum disorder; cognitive flexibility; neuropsychology

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Significant outcomes

- Our findings may help school psychologists screen for possible autism spectrum disorder (ASD) when doing a psychoeducational evaluation and thus reduce the number of cases of ASD initially misdiagnosed with attention deficit hyperactivity disorder (ADHD) as the only disorder.
- Our results can help families and treaters to understand the neurobiology associated with rigid behaviour and allow for better treatment planning.
- Our results can help with creating accommodations for individuals with ASD and comorbid ADHD in both school and work settings.

Limitations

- Since subjects in this study were referred for autism spectrum disorder (ASD), our results may not generalise to other clinical and non-clinical settings.
- The neuropsychological measures utilised did not address the variety of language issues documented in the literature in individuals with ASD nor did it address the results as being a product of the additive/interaction effect of ASD-ADHD. While this paper documents underlying neuropsychological deficits in high functioning adults with ASD, it does not focus on interventions to target these specific deficits. Thus, further research in this area is warranted.

Introduction

Autism spectrum disorder (ASD) describes a prevalent group of neurodevelopmental disorders associated with high morbidity and disability (1). While there is increased recognition of ASD in intellectually capable populations (2), such individuals often experience considerable functional deficits. One potential contributor to the functional deficits in individuals with high functioning ASD (HF-ASD) is a deficit in neuropsychological functioning. Although a number of studies have reported the neuropsychological deficits in autism, our study has a unique focus. The literature has generally focussed on theories of autism rather than using well-normed, easily accessible neuropsychological tests to attempt to find neuropsychological underpinnings that could help in diagnostic screening. One area hypothesised to be an underlying neuropsychological deficit in ASD has been the executive functions. Fein (3) devotes an entire chapter in her book on the neuropsychology of autism. However, since most studies are paediatric, and comparison groups are typically developing controls (4–7), our analysis with adults and a comparison group of ADHD individuals is unique.

A major confounder in studies examining the neuropsychological correlates of ASD is its high comorbidity with ADHD, a disorder with well-documented neuropsychological deficits. Thus, efforts aimed at gaining further understanding of the neuropsychological underpinnings of ASD need to address comorbidity with ADHD. A review of the literature yielded several studies that distinguished the neuropsychological deficits in HF-ASD from those with ADHD (8–14). Ozonoff and Jensen (9) investigated executive dysfunction in children with Tourettes Syndrome, ADHD, or autism. The results showed that the ADHD group had difficulty with inhibition, while the autistic group had greater difficulty with tasks involving flexibility and planning. Nyden et al. (8) found that both ADHD and ASD groups had deficits in inhibition, with the ADHD group also demonstrating limited cognitive flexibility. Geurts et al. (10) investigated cognitive processes in children with ADHD or HF-ASD. They found that the ADHD group had executive functioning deficits (EFDs) associated with inhibition and verbal fluency, while the HF-ASD group had deficits in all domains of executive functioning except interference control and working memory. Specifically, the HF-ASD group had greater deficits on planning and flexibility than the ADHD group. However, Goldberg et al. (11) did not find differences on executive functioning in the areas of response inhibition, planning, and flexibility tasks in ADHD and ASD children. Compared with healthy controls, both groups were impaired in working memory. Johnson et al. (13) used a sustained attention task to examine EFDs in ADHD and HF-ASD groups. They found deficits in response inhibition and sustained attention in the ADHD group, while the HF-ASD group showed dissociation in response inhibition but no sustained attention deficits. This review of the literature depicts a lack of consistency in both the testing procedures utilised and EFDs found in HF-ASD groups across studies, thus demonstrating a need for further research in this area. Furthermore, because these papers did not utilise tests that are commonly used in schools or clinic settings, their results cannot be generalised to assist in broad screening for ASD. As such, utilising commonly used tests to further determine a unique profile in HF-ASD compared with individuals with ADHD is of high importance. The study aimed to complete this assessment using commonly used psychological tests.

A better understanding of the neuropsychological features of ASD has important clinical implications. Considering the well-documented morbidity and disability associated with neuropsychological deficits, this knowledge can help develop appropriate intervention strategies aimed at improving them.

The main goal of this study was to examine the unique neuropsychological presentation in adults with HF-ASD by comparison with adults with ADHD. To this end we compared the neuropsychological profiles of adults with HF-ASD with those of individuals with ADHD and controls of similar age and sex without ASD. We hypothesised that neuropsychological deficits would be more

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common in adults with HF-ASD based on their high utilisation of special education service (8%) (15) as well as their significant levels of unemployment (16). To the best of our knowledge, only two other studies have evaluated the neuropsychological features of individuals with HF-ASD with direct comparison to individuals with ADHD and controls (12,14).

Aims of the study

The aim of the study was to assess the qualitatively and quantitatively different neuropsychological deficits of individuals with ASD from those associated with ADHD.

Methods

Participants

Participants with ASD consisted of consecutively referred adults to a specialised programme for the assessment and treatment of ASD at a university-affiliated hospital. HF-ASD was defined as subjects having an IQ above 80. The adults with HF-ASD had normal IQ (>80) and met DSM-IV (17) diagnostic criteria for autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified (PDD-NOS). Subjects with ASD ranged in age from 18 to 40. All subjects received a neuropsychological assessment, a structured diagnostic interview, and a psychiatric interview. A primary caretaker (if available) also completed the structured diagnostic interview. The diagnosis of ASD was established by a board-certified psychiatrist experienced in evaluating ASD and comorbid psychiatric disorders. The detailed psychiatric diagnostic interview was conducted in two sessions of an hour each with the subject and caretaker (usually parent/s), if available, and also incorporated information from multiple sources when available (psychiatric records, schools, social services). The complete assessment procedure took 8–10 h to complete, and was carried out over multiple sessions for each patient. The subjects with ASD were clinic patients on a variety of medications with only one subject on a stimulant (Concerta). The subjects with ASD did not have any exclusion criteria. *Post hoc* analysis revealed 16 participants with ASD had full ADHD and five participants with ASD had sub-threshold ADHD.

For comparison, we used two non-ASD groups with and without ADHD of similar age and sex. Gender was matched directly and age was matched within a varying range up to 10 years. ADHD comparators were outpatient adults with ADHD aged 19–60 years who met full DSM-IV diagnostic criteria for ADHD on the basis of clinical assessment and confirmed by structured diagnostic interview (18).

Subjects with ADHD were outpatient adults aged 20–40 years. To be included, subjects had to satisfy full diagnostic criteria for DSM-IV ADHD on the basis of clinical assessment and confirmation by structured diagnostic interview. To assess inclusion and exclusion criteria, subjects underwent a comprehensive clinical assessment that included a psychiatric evaluation by a board-certified psychiatrist, structured diagnostic interview, medical history, vital signs, and laboratory assessments (liver function tests, complete blood count, weight, vital signs, and electrocardiogram [ECG]). The structured diagnostic interview used was the Structured Clinical Interview for DSM-IV, supplemented for childhood disorders by modules (DSM-IV ADHD and conduct disorder) from the Kiddie Schedule for Affective Disorder and Schizophrenia for School-Age Children–Epidemiologic Version (19). This interview was selected because it diagnoses both lifetime and current (last month) psychopathology and has been used extensively in clinical and research settings. To have been given a full diagnosis of adult ADHD, the subject must have (1) met full DSM-IV-R criteria (at least six of nine symptoms) for inattentive and/or hyperactive/impulsive subtypes (17) by the age of 7 years as well within the past month (i.e. ADHD-IA, ADHD-HI, and ADHD-C subjects were enrolled); (2) described a chronic course of ADHD symptomatology from childhood to adulthood; and (3) endorsed a moderate or severe level of impairment attributed to the ADHD symptoms.

Control subjects (ages 21–36) were derived from longitudinal family genetic studies of youth of both sexes with and without ADHD (20). We used the Structured Clinical Interview for DSM IV (SCID) (21) supplemented with modules from the DSM-IV modified K-Kiddie Schedule for affective disorders and schizophrenia-epidemiological version (K-SADS-E) (19) to assess childhood diagnoses. We interviewed all subjects asking about symptoms that were present in the past 5 years since the last follow-up, which we termed Interval Diagnosis. The K-SADS-E has a section to rule ASD in or out. Interviewers were blind to baseline ascertainment group, ascertainment site and prior assessments. They had undergraduate degrees in psychology and were extensively trained. κ Coefficients of agreement between interviewers and board-certified child and adult psychiatrists and experienced licensed clinical psychologists were previously reported (median κ for individual disorders = 0.98) (22). A committee of board-certified child and adult psychiatrists and child psychologists blindly reviewed all assessments and resolved diagnostic uncertainties. κ Coefficients

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between individual clinicians and the review committee were previously reported (median κ of individual disorders = 0.87) (22).

For subjects with ADHD and for controls we excluded potential subjects if they had clinically significant chronic medical conditions, abnormal baseline laboratory values, intelligence quotient <80, delirium, dementia, or amnesic disorders, other clinically unstable psychiatric conditions (i.e. bipolar disorder, psychosis, suicidality, autism), drug or alcohol abuse or dependence within the 6 months preceding the study, or a previous adequate trial of MPH. We also excluded pregnant or nursing women. None of the subjects with ADHD were on stimulant medication at baseline when they were administered the testing battery. One control subject was on a stimulant (Concerta), but was asked to wash out before coming in for the evaluation.

Only subjects with available neuropsychological data were included in this analysis. Informed consent was obtained from all individual participants included in the study. The institutional review board approved this study, which has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable standards.

Neuropsychological battery

Wechsler Abbreviated Scale of Intelligence (WASI). Two subtests from the WASI, Vocabulary and Matrix Reasoning, were administered (23). The Vocabulary subtest correlates with knowledge base and the ability to retrieve information from long-term memory. Matrix Reasoning is a test of non-verbal reasoning that requires individuals to look at incomplete patterns and select the missing portion from five options.

Wechsler Adult Intelligence Scale (WAIS-III). All subtests from the Working Memory Index (Digit Span, Letter Number, Arithmetic) and Processing Speed Index (Digit Symbol/Coding, Symbol Search) were administered and individual scores as well as Index scores were computed (24,25). Working Memory measures the individual's ability to manipulate information while holding it in mind. Processing Speed is a measure of speed and accuracy in processing routine information.

Tests of executive functioning. The Delis Kaplan Executive Function System (D-KEFS) (26) including the Colour-Word Interference subtest (Colour Naming, Word Reading, Inhibition, and Switching) and Trail Making (TRAILS) subtest (Number Contrast, Number Sequencing, and Number Letter) were administered. The heart of the D-KEFS Trail Making Test is the Number-Letter Switching task. This task requires switching back and forth between connecting numbers and letters in sequence. The ability to perform this task is considered a classic executive function task of cognitive flexibility. The D-KEFS Colour Inhibition/Switching is another task of cognitive flexibility. This task requires 'switching' between reading words printed in varying colour inks with naming the colour ink (those words are in a black box) on which the ink is printed.

Tests of academic achievement. The Test of Word Reading Efficiency (TOWRE) including the Sight Word and Phonemic Decoding subtests (27) were used as a measure of the individual's ability to pronounce printed words accurately and fluently. The task measures both the ability to sound out words quickly and the ability to recognise familiar words as sight words. The Wide Range Achievement Test-III (WRAT-III) (28) assesses mathematical operations. It requires the individual to compute a wide variety of numerical operations that include mathematical concepts from basic addition and subtraction up through algebra and geometry.

Statistical analysis

For continuous outcome variables a linear regression model was used and for binary outcome variables a logistic regression was used. For each outcome variable pairwise tests were carried out using Tukey adjustments. Any demographic variables that significantly differed between groups were used as covariates in the regression models. Seven subjects were missing SES, and these subjects had their SES imputed. All tests were two-tailed with α set at the 5% level.

Results

Socio-demographic characteristics

Two subjects from the ADHD and control groups were matched to each subject with ASD. Thus, comparisons were made between adult subjects with HF-ASD ($n = 26$), adult subjects with DSM-IV ADHD without ASD (ADHD, $n = 52$) and controls without ADHD or ASD (controls, $n = 52$). As shown in Table 1, with the exception of SES, which was lower in the ASD group, there were no other significant differences in socio-demographic characteristics between the groups. All subsequent tests corrected for SES.

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Table 1. Adult socio-demographic characteristics of probands

	ASD ($n = 26$)	ADHD ($n = 52$)	Controls ($n = 52$)	Statistics	p
Age	27.5 (±6.2)	28.2 (±5.6)	27.5 (±4.1)	$F(2,127) = 0.3$	0.7
Male	20 (76.9%)	40 (76.9%)	40 (76.9%)	$\chi^2 = 0.0$	1
SES	2.1 (±0.9)[b]	3.1 (±1.3)[a]	2 (±0.7)	$F(2,127) = 16.7$	<0.001

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; SES, socioeconomic status.
*ASD *n*: 25–26, ADHD *n*: 47–52, controls *n*: 51–52.
[a]$p < 0.05$ vs. controls.
[b]$p < 0.05$ vs. ADHD.

Table 2. Adult cognitive testing results

	ASD ($n = 26$)*	ADHD ($n = 52$)*	Controls ($n = 52$)*	Statistics	p
WASI					
WASI-Full IQ	108.7 (±11.9)	109.2 (±13.6)	113.2 (±11.5)	$F(2,126) = 1.2$	0.3
WASI-Vocabulary	12 (±3.2)	11.6 (±3.5)	12.2 (±2.6)	$F(2,126) = 0.1$	0.9
WASI – Matrix Reasoning	11 (±1.9)[a]	11.6 (±2.1)	12.4 (±1.7)	$F(2,126) = 4.7$	0.011
WAIS-III					
Working Memory	98.3 (±18.4)[a]	104.8 (±15.1)	113.5 (±16.3)	$F(2,126) = 7.6$	<0.001
Processing Speed	89.1 (±15.3)[ab]	103.1 (±13.2)	108.6 (±14.9)	$F(2,125) = 15.5$	<0.001
Digit Span	9.6 (±3.6)[a]	11 (±3.1)	12 (±3.2)	$F(2,126) = 4.7$	0.01
Letter Number	10.1 (±3.6)[a]	10.8 (±3.2)	12.7 (±3.4)	$F(2,126) = 5.5$	0.005
Arithmetic	9.7 (±3.4)[a]	10.7 (±2.5)	12.2 (±2.6)	$F(2,126) = 7.2$	0.001
Symbol Search	8.7 (±3.7)[ab]	11 (±2.7)	12.2 (±2.7)	$F(2,126) = 12.7$	<0.001
Digit Symbol/Coding	7.1 (±2.7)[ab]	10.2 (±2.6)	10.9 (±3)	$F(2,125) = 15.7$	<0.001
D-KEFS Colour Word Interference					
Colour Naming	6.4 (±3.8)[ab]	9 (±2.7)	10.1 (±2.4)	$F(2,123 = 14.7$	<0.001
Word Reading	8.4 (±3.6)[ab]	10.9 (±2.3)	11 (±2.6)	$F(2, 123) = 8.9$	<0.001
Inhibition	8.3 (±3.9)[ab]	10.3 (±2.9)[a]	12 (±2)	$F(2,121) = 14.8$	<0.001
Switching	8 (±3.9)[ab]	9.8 (±2.9)	11.2 (±2.2)	$F(2,122) = 10.5$	<0.001
D-KEFS Trail Making					
TRAILS-Number Contrast	9.8 (±2.9)	9.7 (±2.7)	10.6 (±2.7)	$F(2,126) = 1.0$	0.4
TRAILS-Number Sequence	7.3 (±3.5)[ab]	10.2 (±2.7)	10 (±3.3)	$F(2,126) = 7.8$	<0.001
TRAILS-Number Letter	7.1 (±4.2)[ab]	10 (±2.8)	10.6 (±2.5)	$F(2,126) = 12.2$	<0.001
WRAT-III Arithmetic	90.5 (±12.5)[a]	96 (±11.8)	102.1 (±15)	$F(2,126) = 6.5$	0.002
TOWRE Sight Word	84.6 (±13.5)[ab]	94.9 (±13.3)	96.2 (±13.1)	$F(2,125) = 6.9$	0.001
TOWRE Phonemic Decoding	85.8 (±12.6)[a]	90.8 (±13)	94.7 (±12.3)	$F(2,125) = 4.2$	0.018

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; D-KEFS, Delis–Kaplan executive function system; SES, socioeconomic status; TOWRE, Test of Word Reading Efficiency; WAIS, Weschler Adult Intelligence Scale; WASI, Weschler Abbreviated Scale of Intelligence; WRAT, Wide Range Achievement Test. Adjusted for Age, SES, and Gender.
* ASD *n*: 24–26, ADHD *n*: 49–52, controls *n*: 51–52.
[a]$p < 0.05$ vs. controls.
[b]$p < 0.05$ vs. ADHD.

Neuropsychological findings

As shown in Table 2, there were no significant differences in Vocabulary or Full Scale IQ of the WASI between groups with those scores being solidly in the average range. Despite the Matrix Reasoning score reaching statistical significance, there is no clinical difference in the 1-point difference in scaled score on this test since the SD is 3. Subjects with ASD were significantly more impaired in Working Memory than controls ($p = 0.035$, <0.001), but not more impaired than subjects with ADHD. However subjects with ASD were significantly more impaired than subjects with ADHD as well as controls in the Processing Speed Index ($p = 0.001$, <0.001), as well as the two subtests that make up this index, including Symbol Search ($p = 0.002$, <0.001), and Digit Symbol/Coding ($p < 0.001$, <0.001). In addition, subjects with ASD were significantly more impaired than both subjects with ADHD and controls on D-KEFS Colour Naming ($p < 0.001$, <0.001), Word Reading ($p = 0.002$, <0.001), and Switching ($p = 0.013$, <0.001), as well as D-KEFS TRAILS-Number Sequence ($p = 0.001$, $= 0.004$) and TRAILS-Number Letter ($p < 0.001$, <0.001). Subjects with

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Table 3. Outcome variables of pairwise tests of cognitive results: estimates and confidence intervals from pairwise models (*significance)

	Controls-ASD	Controls-ADHD	ADHD-ASD
WASI-Full IQ	5.1 (−0.9, 11.0)	2.1 (−3.4, 7.5)	3.0 (−3.4, 9.4)
WASI-Vocabulary	0.3 (−1.1, 1.8)	0.1 (−1.1, 1.4)	0.2 (−1.4, 1.7)
WASI – Matrix Reasoning	1.5 (0.5, 2.4)*	0.6 (−0.3, 1.5)	0.9 (−0.1, 1.9)
WAIS-III			
Working Memory	14.9 (7.2, 22.5)*	4.4 (−2.6, 11.4)	10.5 (2.3, 18.7)*
Processing Speed	20.7 (13.4, 28.0)*	4.9 (−1.7, 11.5)	15.8 (8.0, 23.6)*
Digit Span	2.4 (0.9, 3.9)*	0.4 (−0.9, 1.8)	2.0 (0.3, 3.6)*
Letter Number	2.5 (0.9, 4.1)*	1.0 (−0.5, 2.5)	1.5 (−0.2, 3.2)
Arithmetic	2.4 (1.1, 3.7)*	0.7 (−0.5, 1.9)	1.7 (0.3, 3.1)*
Symbol Search	3.6 (2.2, 5.1)*	0.8 (−0.5, 2.2)	2.8 (1.2, 4.4)*
Digit Symbol/Coding	4.1 (2.7, 5.5)*	0.9 (−0.4, 2.2)	3.2 (1.7, 4.7)*
D-KEFS Colour Word Interference			
Colour Naming	3.7 (2.4, 5.0)*	0.9 (−0.3, 2.2)	2.8 (1.3, 4.3)*
Word Reading	2.6 (1.3, 3.9)*	0.1 (−1.1, 1.3)	2.5 (1.1, 3.9)*
Inhibition	3.7 (2.2, 5.1)*	1.9 (0.5, 3.2)*	1.8 (0.2, 3.4)*
Switching	3.1 (1.7, 4.4)*	0.9 (−0.4, 2.1)	2.2 (0.7, 3.7)*
D-KEFS Trail Making			
TRAILS-Number Contrast	0.8 (−0.7, 2.2)	0.7 (−0.6, 2.0)	0.1 (−1.4, 1.6)
TRAILS-Number Sequence	2.5 (1.0, 4.0)*	−0.5 (−1.9, 0.9)	3.0 (1.4, 4.6)*
TRAILS-Number Letter	3.4 (1.9, 4.9)*	0.3 (−1.1, 1.6)	3.1 (1.5, 4.7)*
WRAT-III Arithmetic	12.2 (5.7, 18.8)*	4.7 (−1.3, 10.6)	7.6 (0.6, 14.6)*
TOWRE Sight Word	11.0 (4.6, 17.5)*	0.3 (−5.5, 6.1)	10.8 (3.9, 17.6)*
TOWRE Phonemic Decoding	8.4 (2.5, 14.3)*	1.1 (−4.2, 6.4)	7.3 (1.0, 13.6)*

ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; D-KEFS, Delis–Kaplan executive function system; SES, socioeconomic status; TOWRE, Test of Word Reading Efficiency; WAIS, Weschler Adult Intelligence Scale; WASI, Weschler Abbreviated Scale of Intelligence; WRAT, Wide Range Achievement Test.

ASD were significantly more impaired than both subjects with ADHD and controls on the TOWRE Sight Word ($p = 0.007$, $= 0.003$) (Table 2). While Working Memory subtests (Digit Span, Letter Number, and Arithmetic) were significantly more impaired in the group with ASD than in controls, they did not reach statistical significance when compared to subjects with ADHD. Subjects with ASD were significantly more impaired than controls but not ADHD subjects in WASI-Matrix ($p = 0.009$), Digit Span ($p = 0.007$), Letter Number ($p = 0.007$), Arithmetic ($p = 0.001$), Inhibition ($p < 0.001$), WRAT Arithmetic ($p = 0.001$), and TOWRE Phonemic Decoding ($p = 0.017$).

Table 3 provides estimates of the differences between groups and the corresponding confidence intervals between the three groups. It is generated directly from the models that made the p values for Table 2. Thus the difference between the groups is not the actual difference but the difference between the model estimates.

Discussion

With the exception of IQ and the Vocabulary subtest of the WASI, significant differences were present in all neuropsychological measures assessed in subjects with HF-ASD in comparisons with controls. In addition, differences were observed in the executive functioning domains of set shifting and processing speed in comparisons between subjects with HF-ASD and subjects with ADHD. These findings support the hypothesis that HF-ASD is associated with severe neuropsychological deficits and that cognitive flexibility and processing speed are specific neuropsychological correlates of HF-ASD that cannot be attributed to comorbid ADHD.

The finding of selective impairment in processing speed and sight word reading in adults with HF-ASD when compared to subjects with and without ADHD is noteworthy. To the best of our knowledge, this is the first time that severe deficits in processing speed and sight word reading have been selectively linked to HF-ASD. This finding expands the literature on neuropsychological correlates of ASD in general and for adults with HF-ASD in particular. Although the phonemic decoding subtest only differed from control subjects as measured by the TOWRE, phonemic decoding is a much more rote, learned task whereas sight word recognition is a more integrative task and thereby more impairing. The overlap in individuals having both processing speed deficits and reading deficits is consistent with the literature (29,30), suggesting that reading problems and processing speed deficits may share an underlying cognitive risk factor.

The significant differences found across several tests assessing cognitive flexibility/shifting with subjects with ASD exhibiting more impairment than both individuals with ADHD and controls, are also noteworthy. Not only were these results statistically significant, they were also significantly below the population mean based on the normative data of the tests utilised, indicating a true area of weakness.

Although previous studies also documented deficits in the area of shifting and flexibility in individuals with HF-ASD when compared with controls (31,32), the literature includes only two other studies using an ADHD comparison group to evaluate cognitive shifting/flexibility in HF-ASD (12,14). Although both of these studies utilised the computerised CANTAB test, Sinzig et al.'s findings were consistent with the present study, whereas Happé et al. did not find cognitive flexibility to differentiate subjects with HF-ASD and subjects with ADHD. Happé et al. (12) studied subjects in two age groups (young and old) and noted that their groups

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may have been too small to show statistical differences. Taken together, these findings suggest that the domain of shifting/flexible problem solving may be an area of executive functioning selectively impaired in individuals with HF-ASD.

Moreover, the finding of selective cognitive inflexibility impairment in adults with HF-ASD is highly syndrome congruent. Rigidity and inflexibility is a core feature of ASD. The DSM-5 describes a markedly restricted repertoire of activity and interests as one of the core features of ASD. This feature is frequently described as being one of the most impairing clinical aspects of these disorders.

Our findings documenting severe neuropsychological deficits in general and cognitive inflexibility and processing speed in particular in adults with HF-ASD are of high clinical and scientific relevance. Considering the morbidity of neuropsychological deficits in general and of executive function in particular, their identification could lead to appropriate academic remediation interventions aimed at mitigating them (33,34). Since educational interventions can vary widely for different neuropsychological deficits, the identification of specific areas of cognitive dysfunction can help customise the educational intervention to the deficit.

Lack of flexibility can cause an individual with ASD to overreact to small environmental changes, struggle to meet changing social demands, or be unable to meet increasingly challenging academic demands. Deficits in processing speed also can have important implications for emotional, social, and educational functioning, and in combination with executive functioning impairments, may be a significant neuropsychological challenge for individuals with ASD. For example, keeping up with the flow and comprehension between people is an area that is affected by deficits in processing speed and may help to partially explain the social deficits in individuals with HF-ASD (7,35). Likewise, the ability to detect cognitive inflexibility in subjects with ASD through neuropsychological testing could enhance diagnostic accuracy as well as treatment and educational recommendations made by neuropsychologists, especially for high functioning individuals. Our findings also suggest that neuropsychological findings showing severe deficits in cognitive inflexibility and processing speed should alert clinicians of the possibility that the individual may have an underlying ASD diagnosis. Finally, although the etiology of cognitive inflexibility remains unknown, preclinical work has linked deficits in cognitive flexibility with alterations in BDNF signalling in animal model (36) opening the possibility of future pharmacological interventions targeting BDNF signalling.

Neuropsychological findings in subjects with ASD could also assist in the development of paradigms for fMRI studies examining the neural underpinnings of these impairments. To date, most of the fMRI paradigms have focused on face recognition, emotional processing and eye tracking, but tasks of processing speed and cognitive flexibility could assist in honing in on key areas of brain dysfunction in subjects with ASD.

The findings from the current study must be considered in light of several weaknesses. Given the limited number of participants with ASD assessed, the present study needs to be replicated with larger samples. Also, the use of the K-SADS in adults was utilised dues to the lack of adult interviews for developmental disorders at the time of the study. Since subjects in this study were referred for ASD, our results may not generalise to other clinical and non-clinical settings. Moreover, because our sample consisted largely of Caucasian subjects, we do not know whether our results generalise to other ethnic groups. Additionally, the neuropsychological measures utilised did not address the variety of language issues documented in the literature in individuals with ASD nor do they address a possibility that the results could be a product of the additive/interaction effect of ASD-ADHD. Furthermore, although this paper documents underlying neuropsychological deficits in high functioning adults with ASD, it does not focus on interventions to target these specific deficits. Thus, further research in this area is warranted.

Despite these limitations, our findings reveal robust neuropsychological deficits in subjects with HF-ASD in comparisons with controls. In addition, the specific differences in the executive functioning domains of set shifting and processing speed, as well the deficits in sight word reading in adults with HF-ASD when compared to subjects with ADHD suggests that these deficits may be specific neuropsychological correlates of HF-ASD. The finding of a unique neuropsychological profile within ASD could have significant implications for identifying individuals at risk for ASD in clinical and academic settings where the tests utilised in this study are commonly administered. However, a first step would be a replication of this work with a larger number of subjects.

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interpretation of data, and drafted and critically revised the article for important intellectual content. Dr. Gagan Joshi contributed substantially to the concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Dr. Pradeep Bhide substantially contributed to the concept and design, analysis and interpretation of the data and drafting of the manuscript. Ms. Amanda Pope contributed substantially to the acquisition of data and drafting of the manuscript. In addition, she provided administrative, technical, or material support. Ms. Maribel Galdo contributed substantially to the acquisition of data and revision of the manuscript. In addition, she provided administrative, technical, or material support. Ms. Ariana Koster contributed substantially to the acquisition of data and drafting of the manuscript. In addition, she provided administrative, technical, or material support. Mr. James Chan substantially contributed to the analysis and interpretation of the data, and drafting of the manuscript. Dr. Stephen V. Faraone substantially contributed to the concept and design, analysis and interpretation of the data, and critically revised the manuscript for important intellectual content. Dr. Joseph Biederman substantially contributed to the concept and design, acquisition of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. In addition, he provided administrative, technical, or material support, and supervision. All authors meet conditions for authorship, and have approved the final version of this manuscript for publication.

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Conflicts of Interest

Dr. Ronna Fried is currently receiving research support from the following sources: Lundbeck. In 2015, Dr. Fried received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses. In previous years, Dr. Fried received research support from NIH and Shire. Dr. Gagan Joshi is supported by the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH) under Award Number K23MH100450. He receives research support from Duke University as a site principal investigator for a multi-site clinical trial and from Pfizer and the Simons Center for the Social Brain as a principal investigator for investigator-initiated studies. He is a co-investigator for clinical trials sponsored by the US Department of Defense and Pamlab, LLC. In 2014, he received an honorarium from the Governor's Council for Medical Research and Treatment of Autism in New Jersey for grant review activities and speaker's honorariums from the American Academy of Child and Adolescent Psychiatry, Massachusetts General Hospital Psychiatry Academy, and the Medical Society of Delaware. In 2013, Dr. Joshi received an honorarium from the Simons Foundation for speaking at the Simons Center for the Social Brain Colloquium Series. In 2013 and/or 2014, Dr. Joshi received research support from NIMH (under K23MH100450), Sunovion Pharmaceuticals, Forest Research Laboratories and Duke University and was a co-investigator on research sponsored by Shire, Merck/Schering-Plough Corporation, ElMindA, and Pamlab, LLC. Dr. Joseph Biederman is currently receiving research support from the following sources: The Department of Defense, Food & Drug Administration, Ironshore, Lundbeck, Magceutics Inc., Merck, PamLab, Pfizer, Shire Pharmaceuticals Inc., SPRITES, Sunovion, Vaya Pharma/Enzymotec, and NIH. In 2015, Dr. Joseph Biederman received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses. He has a US Patent Application pending (Provisional Number #61/233,686) through MGH corporate licensing, on a method to prevent stimulant abuse. In 2014, Dr. Joseph Biederman received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses. He received research support from AACAP, Alcobra, Forest Research Institute, and Shire Pharmaceuticals Inc. Dr. Biederman received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Ingenix, Prophase, Shire, Bracket Global, Sunovion, and Theravance; these royalties were paid to the Department of Psychiatry at MGH. In 2013, Dr. Joseph Biederman received an honorarium from the MGH Psychiatry Academy for a tuition-funded CME course. He received research support from APSARD, ElMindA, McNeil, and Shire. Dr. Biederman received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Shire and Sunovion; these royalties were paid to the Department of Psychiatry at MGH. In 2012, Dr. Joseph Biederman received an honorarium from the MGH Psychiatry Academy and The Children's Hospital of Southwest Florida/Lee Memorial Health System for tuition-funded CME courses. In previous years, Dr. Joseph Biederman received research support, consultation fees, or speaker's fees for/from the following additional sources: Abbott, Alza, AstraZeneca, Boston University, Bristol Myers Squibb, Cambridge University Press, Celltech, Cephalon,

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Cipher Pharmaceuticals Inc., Eli Lilly and Co., Esai, Fundacion Areces (Spain), Forest, Fundación Dr. Manuel Camelo A.C., Glaxo, Gliatech, Hastings Center, Janssen, Juste Pharmaceutical Spain, McNeil, Medice Pharmaceuticals (Germany), Merck, MGH Psychiatry Academy, MMC Pediatric, NARSAD, NIDA, New River, NICHD, NIMH, Novartis, Noven, Neurosearch, Organon, Otsuka, Pfizer, Pharmacia, Phase V Communications, Physicians Academy, The Prechter Foundation, Quantia Communications, Reed Exhibitions, Shionogi Pharma Inc, Shire, the Spanish Child Psychiatry Association, The Stanley Foundation, UCB Pharma Inc., Veritas, and Wyeth. In the past year, Dr. Stephen Faraone received income, potential income, travel expenses and/or research support from Pfizer, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA Pharma, Neurovance, Impax, NeuroLifeSciences. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received income or research support from: Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health*, Oxford University Press: *Schizophrenia: The Facts* and Elsevier, *ADHD: Non-Pharmacologic Interventions*. Dr. Pradeep Bhide, Ms. Amanda Pope, Ms. Maribel Galdo, Ms. Ariana Koster, and Mr. James Chan declare that they have no conflicts of interest.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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